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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/886,135	06/22/2001	Leonid Romanovich Ptitsyn	209873US0	5001

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EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 02/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/886,135	PTITSYN ET AL.	
	Examin r	Art Unit	
	Elizabeth Slobodyansky	1652	

-- Th MAILING DATE of this communication appears on th cover she t with th correspond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) *4-6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed October 30, 2003 amending the specification to insert references to the sequence identifiers, replacing the Sequence Listing and amending claims 1-3 has been entered.

The Sequence listing and the computer readable form thereof filed October 30, 2003 have been entered.

Claims 1-6 are pending.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-3, in Paper filed October 30, 2003 is acknowledged. The traversal is on the ground(s) that "a search and examination of all the claims would not constitute a serious burden upon the Examiner" (Remarks, page 12). This is not found persuasive because the examination of Groups II-III would require additional search of at least classes/subclasses 435/114, 252.3, 252.33 and 536/23.2 that are not required for the examination of Group I as well as additional search of patent and non-patent databases and divergent considerations. Applicants further argue that "should the elected group be found allowable, non-elected process claims that include all the limitations of the allowable product should be rejoined". This is not found persuasive because currently there are no pending claims drawn to process of making or process of use of a mutant N-acetylglutamate synthase of Group I.

The requirement is still deemed proper and is therefore made FINAL.

Claims 4-6 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected Groups II-III, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper filed October 30, 2003.

Response to Amendment

The Declaration under 37 CFR 1.132 by Dr. Leonid R. Ptitsyn filed October 30, 2003 is sufficient to provide the evidence that the sequence of the wild type N-acetylglutamate synthase gene of *E. coli* used in the instant invention is identical to the sequence disclosed under GenBank Accession Y00492.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1, with dependent claims 2 and 3, has been amended to recite the wild type N-acetylglutamate synthase that (B) "is at least 70% homologous to a protein having amino acid sequence defined in SEQ ID NO:16". Applicants indicate that "support for the present amendment may be found on page 9, line 12 to page 10, line 7 and at page 7, lines 17-21" (Response filed October 30, 2003, page 6). While the specification provides support for the mutant N-acetylglutamate synthase that is at least 70% homologous to the wild type (page 7, lines 17-21), the examiner is unable to locate adequate support for a wild type sequence that is at least 70% homologous to SEQ ID NO:16. Thus, there is no evidence that a wild type sequence that is at least 70% homologous to SEQ ID NO:16 was within the scope of the invention as conceived by Applicants at the time the application was filed.

Accordingly, Applicants are required to cancel the new matter in the response to this Office action.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling a mutant N-acetylglutamate synthase (NAGS) having an amino acid sequence obtained by replacement of amino acid residues from 15 to 19 in SEQ ID NO:16 with any one of the amino acid sequences of SEQ ID NOs: 1-4, does not reasonably provide enablement for a mutant NAGS that is desensitized to feedback inhibition by L-arginine, said mutant NAGS obtained by replacement of residues corresponding to residues from 15 to 19 in SEQ ID NO:16 with any one of SEQ ID NOs: 1 to 4 in a wild type sequence that

is at least 70% homologous to SEQ ID NO:16. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7)considered in determining whether undue experimentation is required, are summarized the predictability or unpredictability of the art, and (8) the breadth of the claims.

Factors pertinent to this discussion include predictability of the art, guidance in the specification, breadth of claims, and the amount of experimentation that would be necessary to use the invention.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the great number of mutants broadly encompassed by the claims, *supra*.

The specification teaches four mutants with the requisite properties obtained by replacement of residues 15-19 in SEQ ID NO:16 with SEQ ID NOs:1-4. The specification does not teach any NAGS mutants with the requisite property obtained by replacement of residues corresponding to residues 15-19 in SEQ ID NO:16 with SEQ ID NOs:1-4 in a sequence that is at least 70% homologous to SEQ ID NO:16. Further, it fails to provide information regarding

other combinations of substitute amino acids that would result in a mutant with the requisite characteristics. While there are a great number of possible mutants, it is *a priori* unpredictable as to which mutant will exhibit the claimed property. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

With regard to a mutant NAGS obtained form a sequence that is at least 70% homologous to SEQ ID NO:16, the specification does not support the broad scope of the claims because the specification does **not** establish: (A) regions of the protein structure which may be modified without affecting NAGS activity while desensitizing feedback inhibition by L-arginine; (B) the general tolerance of N-acetylglutamate synthases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any NAGS residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

The amino acid sequence of a protein determines its structural and functional properties, and predictability of what changes in the amino acid sequence can be tolerated and result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Furthermore, while recombinant techniques are available, it is not routine in the art to screen large numbers of peptide mutants where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. Therefore, one of ordinary skill

would require a further guidance in order to make a mutant NAGS with the requisite property other than four disclosed NAGS mutants in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "the amino acid sequence corresponding to positions from 15 to 19 in a wild type N-acetylglutamate synthase" wherein the wild type N-acetylglutamate synthase has an amino acid sequence of (A) SEQ ID NO:16 or (B) a sequence that is 70% homologous to SEQ ID NO:16. The term "corresponding to positions from 15 to 19 in a wild type N-acetylglutamate synthase" having a sequence that is 70% homologous to SEQ ID NO:16" is unclear. It appears that "residues in a sequence that is at least 70% homologous to SEQ ID NO:16 corresponding to residues 15-19 in SEQ ID NO:16" are implied. Furthermore, with regard to SEQ ID NO:16, residues 15-19 are residues 15-19 of SEQ ID NO:16, they do not correspond to themselves.

Claim 1 recites "stringent conditions". The specification defines said conditions by non-limiting examples (page 9, line 19 through page 10, line 6). Because the exact conditions under which a given molecule must hybridize to

SEQ ID NO:15 are not known, it is impossible to determine the metes and bounds of the claim.

The scope of claim 3 is further unclear because the claim is drawn to a mutant NAGS with a sequence that is at least 70% homologous to SEQ ID NO:16 whereas claim 3 depends from claim 1 that recites a wild type sequence that is at least 70% homologous to SEQ ID NO:16.

Response to Arguments

Applicant's arguments filed October 30, 2003 have been fully considered but they are not persuasive.

The 112, 1st paragraph, written description rejection is moot in view of the amendment. The previous 112, 2nd paragraph, is moot in view of the amendment.

With regard to the 112, 1st paragraph, enablement rejection, Applicants argue that "with the present specification in hand, determination of protein sequences that fall within the scope of Claims 1-3 require nothing more than routine experimentation to determine sequence homology and protein activity". Applicants further quote from MPEP § 2164.06 and MPEP § 2164.04 (Response, page 9).

This is not persuasive because while methods to produce mutants of a known sequence are well known to the skilled artisan producing mutants as claimed by applicants (i.e., having NAGS activity wherein feedback inhibition by L-arginine is desensitized) requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of

mutants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute **undue** experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein structure which may be modified without affecting NAGS activity while desensitizing feedback inhibition by L-arginine; (B) the general tolerance of N-acetylglutamate synthases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any NAGS residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory

period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner
Art Unit 1652

January 30, 2004